Endocrine Drugs in Aircrew

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INTRODUCTION

Hormones are molecules that are synthesized and secreted by groups of cells clustered in specific tissues, usually known as glands, and are released into the blood, exerting biochemical effects on target cells at a distance from their site of origin. Hormones are chemical messengers, endogenous compounds that are involved in both intracellular and extracellular communication. The site of action is determined by the presence of specific hormone receptors on or in target cells.

Hormones have diverse molecular structures, as summarized in Table 1.

Historical interest in hormonal effects is ancient;[1,3] the physiological and morphological effects of accidental or intentional castration of man or domestic animals were known to be correlated with the loss of testes. Later, transplanted testes were demonstrated to prevent development of capon characteristics in the castrated rooster, and later still it was shown that testicular extracts, and finally testosterone itself, corrected the deficit. Similar discoveries were made concerning the ovary, the adrenal, and the thyroid, through the classic experiments of surgical extirpation and replacement.

In the beginning, hormonal therapy was developed by using *natural substances* extracted from animal or human organs, but now these have been almost entirely supplanted by *synthetic hormones*.

Worldwide prevalence of endocrine disorders varies significantly. Certain endocrine conditions are among the most prevalent diseases in general medicine, particularly diabetes mellitus, obesity, and thyroid disorders.[4]

In clinical endocrinology practice, the most common endocrine diseases are diabetes mellitus, thyrotoxicosis, hypothyroidism, nodular goiter, diseases of the pituitary gland and diseases of the adrenal gland.

Hormonal therapy is, usually, a substitutive treatment for endocrine disease resulting from inadequate hormone production, faulty transduction of a hormonal message, or, finally and rarely, resistance to hormonal action. Hormones are also widely administered in general and specialty medicine because of desired systemic effects of hormonal compounds, such as the anti-inflammatory action of corticosteroids, the contraceptive action of gonadal steroids, or the antineoplastic action of hormonal antagonists. Indeed, some synthetic hormones are only used for this purpose, since they are not suitable for hormonal replacement.

Aeromedical concerns with the therapeutic use of hormones should be addressed by evaluating the mode of action and side effects of hormonal agents when administered to flying personnel, with the goals of recovery and allowing return to qualification. These issues should be addressed whether a hormone is used for replacement, or for its pharmacologic effect. Aeromedical interest tends to focus on those endocrine disorders that arise in adulthood, since those with endocrine problems at an earlier age are usually screened out of flying training.

This monograph will focus mainly on three hormonal therapeutic agents: adrenal hormones, insulin and thyroid hormones. Hypothalamic and pituitary hormones will not be considered, since they are used primarily in diagnostic procedures, and only very rarely for medical treatment.

ADRENAL HORMONES

Adrenal hormones act in a variety of ways to maintain homeostasis and to aid survival in the face of fight-or-flight situations, fasting, injuries, shock, and other stresses.

The human adrenal consists of an outer cortex, which secretes steroid hormones, and an inner adrenal medulla, an extension of the sympathetic

nervous system, which secretes catecholamines.[5] The adrenal cortex produces three types of steroid hormones: glucocorticoids, influencing glucose metabolism; mineralocorticoids, which regulate Na^+ and K^+ balance; and androgens. The adult adrenal cortex is composed of three zones. The outer *zona glomerulosa*, which expresses the enzyme 18-oxidase, produces aldosterone and is regulated primarily by the renin-angiotensin system rather than by adrenocorticotropic hormone (ACTH) from the pituitary gland. The middle *zona reticularis* and the compact innermost *zona fasciculata* express the enzyme 17α-hydroxylase and produce cortisol and androgens; they are regulated by ACTH, via the hypothalamic-pituitary-adrenal axis.

Biologic Effects of Adrenal Hormones

Cortisol is a glucocorticoid hormone. It promotes gluconeogenesis (conversion of amino acids to glucose) in the liver, and increases protein catabolism to obtain the amino acids needed for gluconeogenesis.[6,7] Cortisol inhibits glucose uptake by muscle and fat, causing insulin resistance, promotes hepatic glycogen synthesis, and increases the blood glucose concentration.[8] In adipose tissue cortisol stimulates lipolysis and release of free fatty acids.[9]

An abnormally increased cortisol level, whether as a result of stress, adrenal hyperproduction, or pharmacologic administration, has many side effects. It stimulates appetite, with increased caloric intake and weight gain, and suppresses inflammation and the immune system.[10] Cortisol inhibits bone formation, and exerts catabolic effects on bone, connective tissue and muscle, causing loss of bone and muscle mass, and thus weakness.[11,12] An excess of cortisol causes altered mood, behavior and cognition, resulting in euphoria, insomnia and even psychosis. Cortisol excess increases blood pressure[13] due to its mineralocorticoid effects in increasing salt and retaining water.

Aldosterone is the principal adrenal mineralocorticoid hormone. It increases Na^+ retention, and urinary K^+ and hydrogen ion (H^+) excretion, by the distal renal tubules and collecting ducts; it also acts on other secretory glands, such as sweat glands, salivary glands, and glands in the intestinal tract.[14,15]

Dehydroepiandrosterone (DHEA) is a weak androgen. It is important in the maintenance of female axillary and pubic hair. Adrenal androgens can cause hirsutism and masculinization of females and prepubertal males.

The important differences among the systemically used corticosteroid compounds primarily relate to duration of action, relative glucocorticoid potency, and relative mineralocorticoid potency. Corticosteroids are classified as short-acting, intermediate-acting, and long-acting on the basis of the duration of ACTH suppression after a single dose equivalent to 50 mg of prednisone. The relative potencies of the corticosteroids correlate with their affinities for the intracellular specific receptors. The observed potency of a corticosteroid is determined not only by the intrinsic biologic potency, but also by the duration of action (Table 2).

Therapeutic Use of Adrenal Hormones

Systemic glucocorticoid therapy is usually employed for its anti-inflammatory and immunosuppressive action;[16] in fact, glucocorticoids inhibit the production or action of many mediators of immunity and inflammation, including interleukin-1, lymphokines, prostaglandins, collagenase, leukotrienes, thromboxanes, serotonin, bradykinin, histamine, and plasminogen activator.[16] The more severe the immune or inflammatory disorder, the more readily can glucocorticoid therapy be justified. Thus, corticosteroids are commonly used in patients with severe forms of systemic lupus erythematosus, sarcoidosis, active vasculitis, asthma, chronic active hepatitis, transplantation rejection, pemphigus, and immune hematologic diseases such as thrombocytopenia, hemolytic anemia, and medullary hypoplasia.[17]

The use of high-dose glucocorticoids for one or two weeks, in absence of a contraindication to therapy, is unlikely to be associated with serious side effects (Table 3).[18,19] A severe, but fortunately rare, exception is a corticosteroid-induced psychosis. Although this complication may occur after only a few days of therapy in patients with no previous history of psychiatric disease, the risk is generally related to the dose and duration of therapy; thus, the smallest possible dose should be prescribed for the shortest possible period.[20]

The side effects of glucocorticoids include the diverse manifestations of Cushing syndrome and hypothalamic-pituitary axis suppression. The latter may occur after withdrawal from treatment with the equivalent of 20 to 30 mg/day of prednisone for as little as five days, and carries a high risk of acute

adrenal insufficiency. For this reason glucocorticoids should be withdrawn gradually, over an interval of weeks to months, with frequent assessment of patients.[21,22]

Glucocorticoids are commonly administered to replace the missing hormones in adrenal insufficiency, acute and chronic (Addison's disease), and in adrenogenital syndromes (Table 4). The adequacy of glucocorticoid and mineralocorticoid replacement is currently best evaluated by the clinical response to therapy.[23] Adequate treatment results in the disappearance of weakness, malaise and fatigue. Anorexia and other gastrointestinal symptoms resolve, and weight returns to normal.[24,25]

Secondary adrenal insufficiency has an excellent prognosis with life-long therapy with glucocorticoids and mineralocorticoids, though there is the ever present risk that adrenal crisis may occur during superimposed physiologic stress.[26]

Aeromedical Considerations

There are no currently available biochemical procedures for assessing the response to treatment of adrenocortical insufficiency. Measurement of plasma cortisol or ACTH levels is of no particular value because of the wide variability of each, while measurement of urine free cortisol levels is likewise of little help. The clinical response is the best measure of the adequacy of replacement therapy. Most patients, appropriately treated, may lead normal lives without significant disability, although the risk of development of acute adrenal insufficiency persists. This complication is almost entirely preventable in previously diagnosed and treated patients, but is higher in patients exposed to relevant and frequent physical or psychological stressors.[27]

Aviation, military or civilian, is a high-performance and high-risk occupation, in which operational or conventional flying activity exposes pilots to stressful events that could represent a real risk, even in a subject with appropriately treated adrenocortical insufficiency. In our opinion adrenocortical insufficiency should be considered not suitable for operational flying, because of the serious risk of complications such as acute adrenal crisis. In aviators who will not be exposed to combat flying, those who receive replacement therapy with adrenocortical hormones may be cleared to return to flying duties. This should follow a grounding period to allow complete resolution of the clinical features of Addison's disease. Even then, it seems wisest to restrict such individuals to dual-piloted aircraft.

INSULIN AND DIABETES MELLITUS

Diabetes mellitus is the most common endocrine problem, with a worldwide prevalence of approximately 5%.[28] Recent advances in understanding the pathogenesis of the various types of diabetes and the mechanisms by which complications occur have allowed more effective methods of prevention and treatment.[29] Despite advances, however, the treatment of diabetes with insulin or oral hypoglycemic agents is still accompanied by the risk of hypoglycemia and of the micro- and macrovascular complications of the disease itself, features of great aeromedical concern when considering the possibility of returning a diabetic pilot to flying status.

Blood glucose concentration is maintained within normal range by the action of hormones from the pancreatic islets, which are dispersed throughout the exocrine pancreas and produce four different hormones, insulin, glucagon, somatostatin and pancreatic polypeptide. Insulin and glucagon, both polypeptides, oppose each other in regulating glucose metabolism. Insulin acts to move glucose into insulin-sensitive tissues, such as liver, muscle and fat, and to enhance the storage of fuels. Its major biochemical effect is anabolic, both by promoting anabolism and inhibiting catabolism.[30] Insulin promotes storage of glucose as glycogen, by increasing the rate of glycogen formation and decreasing the rate of glycogenolysis in both the liver and skeletal muscle.[31] By means of its inhibitory effects on both lipolysis and proteolysis, insulin also promotes the storage of fats and proteins. Glucagon, on the other hand, acts by opposing these actions of insulin. Somatostatin inhibits the secretion of both insulin and glucagon, and thus reduces the effects of both these hormones. In addition to insulin and glucagon, several other hormones contribute to the modulation of carbohydrate metabolism. Most are insulin antagonists, including growth hormone, glucocorticoids, epinephrine and thyroxine.

Insulin is continuously secreted by the pancreatic β cell, at a basal rate in the post-absorptive state (6-12 hours after a meal), at a suppressed rate during prolonged fasting, and in large quantities upon

ingestion of nutrients.[32] The action of both insulin and glucagon are mediated by cell surface specific receptors that bind to each hormone.[33] To maintain normal glucose tolerance, insulin secretion and sensitivity to insulin must be normal; absolute insulin deficiency and/or abnormalities in sensitivity to insulin may lead to diabetes. Primary diabetes is classified as Type 1 or Type 2.

Type 1 diabetes was formerly known as juvenile onset diabetes, or insulin-dependent diabetes mellitus. It is caused by an absolute deficiency of insulin and typically occurs because of autoimmune destruction of the pancreatic β cells in genetically susceptible individuals who are exposed to certain environmental factors. The rate at which this destruction occurs is variable, but if the disease occurs in childhood, the destructive process is rapid. Between 50%-85% of children with type 1 diabetes have antibodies to islet cells (ICA) present in their serum at the time of diagnosis, and some also have insulin antibodies, generated in response to destruction of β cells.[34] The worldwide prevalence of type 1 diabetes varies significantly. The highest prevalence is in Finland, which has a rate two to three times that of the USA. The peak age of onset of type 1 diabetes occurs between the ages of 10 and 16, with a second peak of onset occurring in the 40s.[26] Presenting symptoms typically include the classic triad of polyuria, polydipsia, and polyphagia, attributable to the wasting of glucose in the urine, which also results in weight loss.

Type 2 diabetes was formerly known as adult onset diabetes, or non-insulin-dependent diabetes. Type 2 usually occurs because of abnormalities in both insulin secretion and insulin action. The result is that glucose production from the liver increases, and glucose uptake into tissues decreases. The hyperglycemia that ensues exacerbates the problem by leading to further impairment of β cell function and insulin action.[35] Type 2 diabetes has a strong genetic component,[26] but its development is profoundly influenced by environmental factors such as obesity and lack of exercise, which increase insulin resistance. Prevalence of type 2 diabetes varies from 6% to 10%.[36]

Treatment of Diabetes

The aims of diabetes therapy are twofold: firstly to correct the symptoms of diabetes, and secondly to normalize plasma glucose concentration as much as possible to prevent the long-term complications of diabetes.[37]

Patients with type 1 diabetes have an absolute insulin deficiency, and therapy is designed to replace insulin in as physiologic a manner as possible. Insulin must be present throughout the day at a level sufficient to maintain normal plasma glucose concentrations under a variety of circumstances. The insulin preparations commonly used for treatment of diabetes are listed in Table 5. They have different times of peak effect and duration of action, and may be used alone or in combination. Patients with type 1 diabetes are totally dependent on exogenous insulin, with a significantly increased risk of serious ketoacidosis and hypoglycemic reactions.

In type 2 diabetics, diet and exercise are generally employed as the first line of therapy, unless patients are very symptomatic or significantly hyperglycemic. If the patient is obese, as is frequently the case, the primary goal of diet therapy is simply caloric reduction to achieve weight loss, which decreases insulin resistance. If adequate glycemic control cannot be obtained, pharmacologic therapy is added. Oral hypoglycemic agents are administered first (Table 6). Since the disease typically worsens over the course of time, most patients eventually find oral medication to no longer be sufficient; at that point, oral medications can be combined, or insulin can be added.

Management

The ideal management of an individual with diabetes would result in no symptoms attributable to diabetes; prevention of acute complications; prevention of microvascular and neuropathic disease; and, a life expectancy equal to nondiabetic individuals. Unfortunately ideal management is currently not attainable; the best that can be done is to strive for minimal morbidity and mortality.

Diabetes mellitus is associated with both acute and chronic complications. Acute complications include marked hyperglycemia, ketoacidosis, hyperosmolar nonketotic coma, and infections, to name a few. Chronic complications include microvascular, macrovascular and neuropathic manifestations, which usually require a number of years to become clinically evident.[38]

Glycemic control that maintains plasma glucose values at <200 mg/dl will generally eliminate the symptoms of polydipsia, polyuria, polyphagia, weight loss and increased fatigue. Plasma glucose levels at 150-165 mg/dl are usually associated with a sense of well-being and good health. Preventing

chronic microvascular and neuropathic complications, on the other hand, probably requires normoglycemic or near-normoglycemic regulation. Minimizing macrovascular disease also requires addressing other risk factors, including smoking, hypertension, plasma triglycerides and low/high-density lipoprotein cholesterol, in addition to glucose control. The maintenance of plasma glucose at near-physiologic levels using intensive insulin regimens will prevent the long-term complications of diabetes,[39] but will simultaneously expose patients to a greater risk of hypoglycemia, which in extreme cases can have a mortality rate as high as 10%,[40] and invariably has profound implications regarding cognitive function.

Aeromedical Concerns

Symptomatic diabetes is not suitable for flying duties. Symptoms as nausea, polyuria, polydipsia, fatigue, and blurred vision are usually disabling, and at a minimum alter the aviator's capabilities. Furthermore, the condition is acutely unstable. Untreated diabetic aviators are not fit to fly.

The most relevant problem in aircrew on diabetic therapy is the difficulty of maintaining control of blood glucose, a problem which may be increased by stressful events, due to the action of stress hormones.[40] Intensive treatments reduce diabetes complication, but expose the patient to three times greater risk of developing hypoglycemia than control groups receiving standard treatment. Symptoms of hypoglycemia[41] usually begin when the plasma glucose concentration falls to 45-50 mg/dL (normal: 70-110 mg/dL) and can be divided into two categories:

- Adrenergic symptoms, due to excessive secretion of epinephrine in response to hypoglycemia, which consist of sweating, tremor, tachycardia, anxiety and hunger.
- Neuroglycopenic symptoms, caused by dysfunction of the central nervous system due to hypoglycemia, which include dizziness, headache, clouding of vision, blunted mental activity, loss of fine motor skill, confusion, abnormal behavior, convulsions and loss of consciousness.

Hypoglycemia is the major concern in the care of diabetes treated with insulin, and is a more profound concern in the diabetic aviator. Some authors have proposed allowing continued flying for diabetics at low risk for hypoglycemia with regular blood monitoring during a limited duty period, and assigning such aviators to flight duties with geographic and operational flying limitations.[42] While such efforts to decrease losses of trained aviation personnel are readily understandable, diabetic aviators are subjects at risk, who require tight medical monitoring by their flight surgeon and an endocrinologist, repetitive ophthalmologic evaluation, and regular screening for cardiovascular and renal complications. In our opinion, type 1 diabetics should be considered not suitable for flying duties because of the serious risk of acute complications which in the aviation environment are particularly likely to be lethal.

The case of type 2 diabetics is different, particularly those controlled by diet and exercise, where no flying restrictions are usually imposed. As compared with insulin, oral agents result in more stable control, and, particularly in the case of biguanides are associated with a low risk of acute complications.[43] In selected cases, non-combat pilots could be returned fit to fly with some limitations; waiver authorities must individually determine the level of risk acceptable for continued flying duties, and which waiver restrictions should be applied.

THYROID HORMONES

The thyroid gland synthesizes two hormones, thyroxine (T_4) and triiodothyronine (T_3), which are iodinated amino acids. Although T_3 is the physiologically active hormone, most of the thyroid hormone secreted from the normal thyroid is T_4; less than 20% of total T_3 is produced in the gland, while the remaining 80-90% is derived from the deiodination, by desiodase enzymes, of T_4 in peripheral tissues such as liver, kidney and muscle.[44] Administration of T_4 or T_3, or the disease induced or iatrogenic absence of these hormones, produces general effects on metabolism, and has particular effects on specific organ systems.

Thyroid Hormone Action

Thyroid hormone action at the cellular level is initiated by the binding of thyroid hormone to a specific nuclear receptor.[45] Thyroid hormones exert major effects on growth and development. In all tissues except the brain, spleen and testis, they elevate O_2 consumption, resulting in increased heat production. They have marked chronotropic and inotropic effects on the heart, with low cardiac output, bradycardia, and slow myocardial contraction and relaxation being characteristic of hypothyroidism. Many actions of thyroid hormones, particularly on the cardiovascular system, are similar to those induced by catechol-

amines, which may be at least partially explained by the finding that thyroid hormones increase the number of catecholamine receptors in heart muscle cells.[46] Thyroid hormones are necessary for normal function of respiratory centers; hypoventilation with hypoxia is a consequence of hypothyroidism.

Thyroid hormones affect the metabolism and clearance of various hormones and pharmacologic agents.[47] Steroid hormone clearance is increased. Serum prolactin levels are increased in about 40% of patients with primary hypothyroidism. Insulin requirements in diabetics are frequently increased in hyperthyroidism. Thyroid hormones are necessary for normal LH and FSH secretion. In hypothyroidism, anovulation and menstrual disturbances may occur. Parathyroid hormone action may be diminished in hypothyroidism.

Clinical Syndromes

Since hyperthyroidism is an unstable clinical condition which requires definitive treatment, its management in the aviator differs little from the clinical patient, and it will not be considered further.

Hypothyroidism is a clinical, biochemical and metabolic syndrome resulting from inadequate thyroid hormone production with sub-normal thyroid hormone concentration, or from faulty transduction of the thyroid hormone message, which is characterized by a generalized slowing down of metabolic processes.[46] In adulthood, the disease is largely limited to this metabolic slowing, and the symptoms are usually reversible with therapy. Common features of hypothyroidism include easy fatigability, coldness, weight gain, constipation, menstrual irregularities and muscle cramps. Physical findings include a cool, dry skin, puffy face and hands, hoarse, husky voice, and slow reflexes. Hypothyroidism causes impairment of the cardiovascular system, with bradycardia and cardiac enlargement; of pulmonary function, characterized by shallow, slow respirations and defective ventilatory responses to hypercapnia; of intestinal peristalsis, resulting in chronic constipation; and of renal function, with decreased glomerular filtration rate and impaired ability to excrete a water load.[48] Many patients complain of symptoms referable to the neuromuscular system, such as severe muscle cramps, paresthesias and muscle weakness. Central nervous system symptoms may include chronic fatigue, lethargy and inability to concentrate.

Hypothyroidism, as well as other thyroid diseases, is more frequent in women, with a female/male ratio of 5/1. It may occur as a transient complication of the late phase of subacute thyroiditis, or more commonly as a permanent result of chronic thyroiditis (Hashimoto's thyroiditis). Hypothyroidism commonly occurs after ablative therapy, such as administration of radioactive iodine or subtotal thyroidectomy in Graves' disease, and occasionally after surgical treatment of nodular goiter or thyroid carcinoma.

Treatment of Hypothyroidism

Hypothyroidism is treated with synthetic thyroid hormones levothyroxine (L-T_4) and triiodothyronine (T_3) (Table 7), both available in pure and stable form. Desiccated thyroid, typically of porcine origin, is unsatisfactory because of its variable hormone content and frequent side effects. L-T_4 is converted in the body in part to T_3, so that both hormones become available even though only one is administered. T_3 therapy is unsatisfactory because of its rapid absorption and rapid disappearance from the bloodstream. The half-life of L-T_4 is about 8 days, so it need be given only once daily. Replacement doses of L-T_4 in the average adult average about 1.6 mcg/kg/d, with the goals of resolution of the features of hypothyroidism, and normalizing plasma TSH and thyroid hormone levels. Generally, only two thirds of the oral dose of the preparation is absorbed, but blood levels are easily monitored by following the free thyroxine and TSH levels.[49]

Aeromedical Concerns

The impact that hypothyroidism has on an aviator depends to some extent on the clinical stage and the treatment that is being used. Although clinical evidence of hypothyroidism varies considerably, physical and laboratory assessment of thyroid function usually allows the patient to be categorized as having either "overt" or "subclinical" hypothyroidism.[48] In the former, patients present with signs and symptoms indicating abnormal function of one or more organ systems, whereas in the latter, patients appear clinically normal, but display elevated serum TSH concentration, typically with normal or only slightly depressed levels of thyroid hormone.

The management of overt hypothyroidism is relatively straightforward; patients must be treated with replacement thyroxine therapy. Subclinical hypo-thyroidism, on the other hand, should not be viewed as a benign laboratory aberration despite the

absence of findings. In approximately 8% of these patients, the disease progresses to overt hypothyroidism.[50] Moreover, subclinical hypothyroidism may have significant effects on some peripheral target organs at an early stage; in particular, it appears to be a risk factor for atherosclerotic coronary heart disease. Of additional concern in aviators, it may also cause marked impairment of some cognitive functions such as memory and behavioral changes.[51-53]

Thyroid hormone metabolism may be altered in strenuous and extended flight.[27] Probably due to relative hypoxia, symptoms of subclinical hypothyroidism are more likely to evince themselves in the aviation environment. In view of the effect of thyroid hormone on oxygen consumption, this is not surprising. For instance, in such situations the latency of visual evoked potentials has been shown to be prolonged, and electroencephalography has shown a decreased amplitude and loss of alpha rhythm. Furthermore, there has been demonstrated impairment in memory and behavior in subclinical hypothyroidism, reinforcing that patients with subclinical hypothyroidism should be treated with adequate doses of L-T_4.[54]

After beginning replacement therapy with L-T_4, patients will be normo-metabolic in two or three weeks. Blood level evaluation of thyroid hormones and TSH, and perhaps dynamic testing with TRH, should be required to confirm euthyroidism before returning the aviator as fit to fly.

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Table 1. Categorization of Hormones by Molecular Structure

Peptides and Proteins		Steroids	Amines
Glycoprotein	**Polypeptides**		
Follicle-stimulating hormone (FSH) Human chorionic gonadotropin (hCG) Luteinizing hormone (LH) Thyroid-stimulating hormone (TSH)	Adrenocorticotropic hormone (ACTH) Angiotensin Calcitonin Cholecystokinin Erythropoietin Gastrin Glucagon Growth hormone Insulin Insulinlike growth peptides Melanocyte-stimulating hormone (MSH) Nerve growth factor Oxytocin Parathyroid hormone Prolactin Relaxin Secretin Somatostatin Vasopressin (ADH)	Aldosterone Cortisol Estradiol Progesterone Testosterone Vitamin D	Epinephrine Norepinephrine Thyroxine (T_4) Triiodothyronine (T_3)

Table 2. Biological Characteristics of Selected Corticosteroids

Duration of Action	Glucocorticoid Potency	Equivalent Glucocorticoid Dose (mg)	Mineralocorticoid Activity
Short-Acting			
Cortisol	1	20	Yes
Cortisone	0.8	25	Yes
Prednisone	4	5	No
Prednisolone	4	5	No
Methylprednisolone	5	4	No
Intermediate-Acting			
Triamcinolone	5	4	No
Long-Acting			
Betamethasone	25	0.60	No
Dexamethasone	30	0.75	No

Table 3. Complications and Side Effects of Corticosteroids

Cardiovascular
- Hypertension
- Congestive heart failure

Gastrointestinal
- Peptic ulcer disease
- Pancreatitis

Endocrine-Metabolic
- Iatrogenic Cushing
- Acne, hirsutism, menstrual irregularities
- Suppression of growth
- Diabetes mellitus
- Sodium retention, hypokalemia
- Secondary adrenal insufficiency

Ophthalmic
- Posterior subcapsular cataracts
- Glaucoma

Musculoskeletal
- Osteoporosis
- Myopathy

Neuropsychiatric
- Psychosis
- Pseudotumor cerebri

Immune, Infectious
- Decreased inflammatory responses
- Susceptibility to infections

Table 4. Adrenal Insufficiency Replacement Therapy

- CORTISOL, 15-20 mg in AM and 10 mg at 4-5 PM
- FLUDROCOTRISONE, 0.05-0.1 mg orally in AM
- CLINICAL FOLLOW-UP
- PATIENT EDUCATION TO INCREASING CORTISOL DOSAGE DURING "STRESS"

Table 5. Characteristics of Insulin Preparations

INSULIN	ONSET OF ACTION (hr)	PEAK OF ACTION (hr)	AVERAGE DURATION OF ACTION (hr)	MAXIMUM DURATION (hr)
Regular	0.5 – 1	2 – 3	3 – 6	4 – 8
Lispro	immediate	1 – 2	2 – 4	4
Neutral Protamine Hagedorn	2 – 4	4 – 10	10 – 16	14 – 18
Lente	3 – 4	4 – 12	12 – 18	16 – 20
Ultralente	6 – 10	none	18 – 20	18 - 24

Table 6. Oral Hypoglycemic Agents

DRUGS	SITE OF ACTION	ACTIONS	SIDE EFFECTS
Sulfonylureas: Glyburide Glipizide Glimepiride Tolazamide	Pancreas	Increase insulin secretion	Hypoglycemia, weight gain
Biguanides: Metformin Fenformin	Liver	Decrease hepatic glucose production	Anorexia, diarrhea and lactic acidosis
Inhibitors of Starch digestion: Acarbose Miglitol	Intestine	Delay starch and sucrose digestion, delay glucose absorption	Flatulence, diarrhea, abdominal pain
Thiazolidenediones: Troglitazone	Muscle and liver	Increase muscle glucose uptake, decrease liver glucose output	Increase plasma Volume, liver toxicity

Table 7. Thyroid Preparations for Replacement Treatment

	Average Daily Adult Dose (mg/d)	Comment
Levothyroxine ($L\text{-}T_4$)	150 μg	Best preparation
Triiodothyronine (T_3)	50 μg	Difficult to monitor, multiple doses required
Desiccated thyroid	90 mg	Variable potency